service. To carry out this review, the Institute of Medicine Committee on Health Effects Associated with Exposures During the Gulf War was formed in 1998 and held its first meeting in January 1999 (IOM, 1998a).

Initial research recommendations from the review panels included:

- epidemiological research to compare prevalence rates of illnesses in Gulf War veterans with appropriate control populations;
- research to examine groups of symptomatic Gulf War veterans more closely with neuropsychological and psychological tests; and
- research on specific risk factors such as stress, pesticides, depleted uranium, and Leishmaniasis (DSB, 1994; NIH, 1994a,b; IOM, 1996b; PAC, 1996a).

More recent research recommendations include:

- research into the long-term effects of low-level exposure to chemical warfare agents, alone and in combination with exposure to other Gulf War health risk factors including stress, pesticides and pyridostigmine bromide;
- epidemiological research on groups of U.S. troops known to be in the vicinity of Khamisiyah when low-level exposure to nerve agents may have occurred;
- research emphasis should include investigations of the causes, methods of prevention, and methods of treatment of musculoskeletal conditions and stress-related disorders (PAC, 1996b, 1997).

The Institute of Medicine established the Committee on Measuring Health Status of Persian Gulf Veterans in 1998 to identify important research questions regarding Gulf War illnesses and develop research designs and methods to address the questions (IOM, 1998b). The committee held a workshop in May 1998 (IOM, 1998c), but the committee's findings and recommendations are not yet available.

Overviews of research results and ongoing research on illnesses among Gulf War veterans are presented in sections 5 and 6 and Appendices C and D of this document.

4. Overview: U.S. Government-Supported Research on Gulf War Illnesses

In response to Public Law 102-585, President Clinton, in August, 1993, named the Secretary of Veterans Affairs to coordinate executive branch-funded research on the health consequences of the Gulf War. The Persian Gulf Veterans Coordinating Board (PGVCB) was formed in January, 1994 to coordinate interagency efforts in research, clinical care, disability compensation, resource allocation, and information dissemination. The Secretaries of the DoD, the DVA, and the DHHS chair the PGVCB. The RWG was established to assess the state and direction of research, identifying gaps in factual knowledge and conceptual understanding, identify testable hypotheses, recommend research directions for participating agencies, review research concepts as they are developed, and collect and disseminate scientifically peer-reviewed information (RWG, 1998).

In the 1994-1997 period, the RWG coordinated U.S.-government sponsorship of 121 research projects pertaining to illnesses in Gulf War veterans (RWG, 1998). New projects were funded in 1998.

As reported in the March 1998 RWG Annual Report to Congress, 39 of the 121 projects were completed through February, 1998. Total funding for research on Gulf War illnesses in the DoD, DVA, and the DHHS (in millions of dollars) was $7.1 in 1994, $17.3 in 1995, $18.8 in 1996, $34.2 in 1997, and $37.9 (projected) in 1998 for a total of $115 million to date (RWG, 1998).

In 1995 and 1996, the RWG established six focus areas of research:

- Symptoms/General Health
- Brain and Nervous System
- Reproductive Health
- Pyridostigmine Bromide
- Environmental Toxicology
- Leishmaniasis.

In response to the 1996 DoD announcement that U.S. troops demolished an Iraqi weapons bunker at Khamisiyah in March of 1991 and that certain troops may have experienced low-level exposure to nerve gas, the RWG (1998) added two additional focus areas related to possible health effects from low-level exposures to chemical weapons agents:

- epidemiological research on health outcomes in troops potentially exposed to sarin at Khamisiyah: and
- research on potential health effects from low-level, sub-clinical exposures to chemical warfare nerve agents, alone and in combination with exposure to other agents.

Ongoing, U.S. Government-funded research projects related to Gulf War illnesses and of interest to the focus of the current research-planning conference are briefly described in Appendix D and include:

- seven projects related to multiple symptom illnesses such as *multiple chemical sensitivity* and chronic fatigue syndrome;
- six projects (two human studies and four animal studies) related to *genetic differences in susceptibility to chemicals or stress*;
- thirteen projects (all animal studies) related to *toxic effects from mixtures of chemicals and other risk factors* (e.g., effects of sarin, pyridostigmine bromide and DEET, alone or in combination, on neurobehavior and immune function in rats);
- four projects related to *treatment of Gulf War symptoms* (two clinical trials of antibiotic treatment, one clinical trial examining cognitive behavioral therapy and aerobic exercise; and one animal study examining behaviorally-active drugs to modify behavior in mice);
- eight projects (three epidemiological studies and five animal studies) related to *toxicity of low-level, subclinical exposures to chemical warfare agents* (all but one project is related to exposure to nerve agents; the other examines possible DNA effects from nitrogen mustard);

- six projects (one human controlled-exposure study and five animal studies) related to *toxicity of pyridostigmine bromide*;
- and numerous clinical and epidemiological studies related to *assessment and definition of Gulf War illnesses* and quantification of *disease prevalence and associations between chemical exposures and disease*.

5. Gulf War Illnesses: Research Results and Ongoing Research

This section discusses results from research related to illnesses in Gulf War veterans and relationships of the results to ongoing research projects. Included in the discussion are results from mortality and hospitalization studies, studies of self-reported symptoms in Gulf War-deployed and non-deployed veterans, studies of neurophysiological and neuropsychological variables in symptomatic Gulf War veterans, studies of health effects from mixtures of chemicals used in the Gulf War and other risk factors, studies of genetic differences in susceptibility to environmental agents, studies of multiple chemical sensitivity in Gulf War veterans, and studies of treatment of Gulf War veterans with non-specific chronic symptoms of ill health. Appendix C: *Research on Gulf War Illnesses: Description and Evaluation of Selected Studies* and Appendix D: *Ongoing Research Related to Illnesses Among Gulf War Veterans* provide additional details.

Mortality and Hospitalization Studies

Large-scale studies are available comparing the following in active-duty U.S. military personnel who served in the Gulf War with active-duty personnel who did not serve in the Gulf :

- rates of mortality (Writer et al., 1996; Kang and Bullman, 1996, 1997);
- rates of general hospitalizations (Gray et al., 1996);
- rates of hospitalizations for unexplained illnesses (Knoke and Gray, 1998);
- rates of hospitalization for testicular cancer (Knoke et al., 1998); and
- rates of general birth defects and a specific birth defect, Goldenhar syndrome (Cowan et al., 1997; Aranata et al., 1997).

The mortality rate studies found no differences between Gulf War-deployed and non-deployed personnel, except for a higher rate of mortality from unintentional injuries (i.e., accidents, in particular motor vehicle accidents) in deployed personnel (Writer et al., 1996; Kang and Bullman, 1996, 1997). The hospitalization studies, which focused on discharge rates from U.S. military hospitals, found no consistent evidence for increased hospitalizations in Gulf War-deployed personnel (Gray et al., 1996; Knoke and Gray, 1998; Knoke et al., 1998). The studies of children of deployed-personnel born in U.S. military hospitals found no statistically significant increase in